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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/634,114	08/04/2003	Gary D. Glick	UM-08192	6392

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EXAMINER	
EBRAHIM, NABILA G	
ART UNIT	PAPER NUMBER
1618	
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03/03/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/634,114	GLICK, GARY D.	
	Examiner	Art Unit	
	Nabila G. Ebrahim	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 13-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 13-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/20/2008 and 11/17/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/17/2008 has been entered.

Information Disclosure Statement

Receipt of IDS dated 2/4/2009 is acknowledged.

Status of Claims

Claims 1, 12-24 are pending in the application.

Claims 22-24 are new.

Status of Office Action: non-final

Priority

Applicant claims benefits of provisional applications 60131761 and 60165511 both having priority dates in 1999. Reviewing the said applications showed that both applications are not related to stents or vascular diseases. Thus, the priority is denied at least to the year 2000 and consequently, relying upon references disclosed in the year 1999 is proper.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1, and 13-24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al (Synthesis of 3-Substituted 1, 4-Benzodiazepin-2.ones, Braz. Chem., foc., Vol. 9, No. 4, 375-379, 1998. **provided by Applicant in the IDS dated 4/6/05);** (hereinafter Kim) in view of Punegova et al. RU 2096044 (abstract), and in view of Soykan et al. US 6824561 (Soykan), in view of Ramdas, Benzodiazepine Compounds as Inhibitors of the Src Protein Tyrosine Kinase: Screening of a Combinatorial Library of 1,4-Benzodiazepines, Archives of Biochemistry and Biophysics, Vol. 368, No. 2, August 15, pp. 394-400, 1999 (Ramadas) and further in view of Alexander Levitzki, Protein Tyrosine Kinase Inhibitors as Novel Therapeutic agents, Pharmacology, Ther. Vol. 82, Nos. 2-3, pp.231-239, 1999 (Levitzki).

Kim teaches a novel BZ-423 compound that is benzodiazepine analog, see abstract. The reference teaches the recited compound is sharing all the pharmacological activities with benzodiazepine, see page 375.

Kim does not disclose the use of the disclosed compounds in a stent.

Punegova teaches melatonin based implant composition for controlling biological rhythm in animals. The composition comprises (in wt %): 10-40 melatonin, 55.5-89.95 Tsiakrin-EO (ethylcyanoacrylate-based polymer), 0.05-4.5 plasticiser (phthalate, alkylcyanoacetate or triacetin). A psychotropic drug e.g. phenothiazine or benzodiazepine derivatives is optionally included in an amount of 7-25 wt%. Note that stent are types of implants (as evidenced by Kullinan et al. US 6147092 who teaches that an example of local delivery by an implant is the use of a stent. Stents are designed to mechanically prevent the collapse and reocclusion of the coronary arteries. Incorporating a pharmaceutical agent into the stent delivers the drug directly to the proliferative site, see col. 11, lines 16+).

It would have been obvious to one of ordinary skill in the art to deliver the compound recited in claim 1 (Bz-423) in a stent because Punegova teaches that Benzodiazepine

derivatives can be included in an implant which can be a stent. It would have been obvious because a person of ordinary skill has good reason to try different and recently known derivatives of Benzodiazepines for elution in a stent, it is likely that bz-423 in a stent is not innovative but of ordinary skill and common sense.

Neither of the references teaches delivering the combinations of the drugs recited in the instant claims through the stent.

Soykan teaches implantable system with drug-eluting cells for on-demand local drug delivery. The imlpantable system is a stent comprising a composition which in turn comprises drugs such as nitric oxide, prostaglandin H synthase (to restore an endogenous inhibitor of platelet aggregation and vasoconstriction (col. 9, lines 31+), antiplatelets (col. 10, line 27), anti-inflammatory (col. 12, line 4). The reference discloses that it was known in the art to use stents for delivering a drug e.g., antiplatelet agents, anticoagulant agents, antimicrobial agents, antimetabolic agents (col. 1, lines 56+) and also that stents seeded with autologous endothelial cells were known in the art since the year 1989 (col. 2, lines 12+).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine any of the drugs disclosed by Soykan with the benzodiazepine compound recited in claim 1 to enhance the effect of the drug comprised in the stent implanted according to the condition being treated. The skilled artisan would expect success since these drugs were known previously in the art to be effective when delivered from a stent. Accordingly, the whole invention was prima facie obvious to one of ordinary skill in the art. Regarding new claim 21 which recites that the mammalian subject is a human, it is noted that the generic disclosure of Punegova of “a based implant composition for controlling biological rhythm in animals” does not exclude humans.

The new amendments to the claims and new claims 22-24 are rejected as follows:

None of the references teaches the use of BZ-423 alone in stent or why a person of ordinary skill would prefer to sue the compound solely to treat restenosis and none of the references teaches the drug concentration needed to achieve said function.

Ramdas teaches benzodiazepine compounds as inhibitors of the Src protein tyrosine kinase. The benzodiazepine compounds were found to have IC_{50} of 73μM (to explain IC_{50} "half maximal inhibitory concentration" is the measure of the effectiveness of a compound in inhibiting biological or biochemical function). Thus, it is noted that the IC_{50} can lead to an estimation of the concentration of the compound required for the treatment of a disease and this concentration can be adjusted by routine testing known by people of ordinary skill in the art.
None of the references teaches the relation between protein tyrosine kinase and restenosis.

Levitzki teaches that Protein tyrosine kinases (PTKs) play a key role in normal cell and tissue development. Enhanced PTK activity is intimately correlated with proliferative diseases, such as cancers, leukemias, psoriasis, and restenosis (abstract).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the BZ-423 solely in a stent used to treat restenosis since Levitzki demonstrates that the PTKs activity is intimately correlated with proliferative diseases such as restenosis and Ramdas teaches that benzodiazepine compounds are inhibitors of the Src protein tyrosine kinase. Thus the entire claimed invention was prima facie obvious to a person of ordinary skill in the art at t he time the invention was made and the artisan would expect success in having a drug eluting stent wherein the drug-eluting stent comprises benzodiazepine compound such as BZ-423 with or without other drugs known to treat restenosis.

Response to Arguments

Applicant's arguments filed 11/17/2008 have been fully considered but they are not persuasive. Applicant argues that:

- Applicant argues that benzodiazepine is sharing pharmacological activities with benzodiazepine stating that Kim makes no comparison whatsoever between the biological activity of Bz-423 and the biological activity of other benzodiazepine compounds.

To respond: this was not found persuasive because Applicant did not argue the pharmacological differences Applicant believes between the structure recited in claim 1 and benzodiazepine disclosed by Kim. Note also that new reference Ramdas discloses the same compounds.

- Applicant argues that certain benzodiazepine compounds have psychotropic effects. However, instant application describes in example 22 and 23 the compound Bz-423 binds to mitochondrial f1f0-ATPase. Applicant thinks that proliferative effects of Bz-423 are due to binding of the compound to mitochondrial F1F0-ATPase.

To respond: the compounds disclosed by Kim and Ramdas are used in treating diseases other than psychotic disorders. In addition, Bz-423 should accrue its effects regardless of the intent of its use because a compound and its properties are not separable.

- Applicant respectfully submits that the subject matter of claim 1, as amended, which is directed to "a drug-eluting stent media coated on a vascular stent" where the stent media comprises the F1F0-ATPase inhibitor Bz-423 " in an amount effective to inhibit restenosis in a subject," would have not been obvious to the skilled artisan based on art applied in the Office action.

To respond: as the claims amended the drug eluting media in coated on a vascular stent is disclosed by Soycan (see col. 6, lines 48+ and col. 10, lines 62+ bridging to col. 11, lines 1+).

Regarding requiring a disclosure of F1F0-ATPase in the prior art, it is noted that instant claims do not recite this limitation. Finally, new references, Ramdas and Levitzki disclose the reason for using benzodiazepines disclosed in the instant claims in a disorder such as restenosis.

- The teachings of Punegova and Kim provide no reason for the skilled artisan to add compound Bz-423 to the melatonin-based implant of Punegova. Further, Applicant argues that modifying the melatonin-based implant of Punegova for use in a vascular stent could have undesirable consequences due to the melatonin, which, according to Punegova, is present in concentrations sufficient to artificially alter development of the subject.

To respond: Kim discloses the Bz-423, Punegova is relied upon for demonstrating that comprising benzodiazepines in a stent is not novel and that it was obvious to a person of ordinary skill in the art at the time the invention was made. Note that comprising the benzodiazepine compound in a stent should affect the restenosis regardless of the effect of melatonin. Note also that the stent is not made of melatonin, however, the drug is comprised in a carrier and can be included or excluded as needed in treating a specific condition. Indeed the reference obviates the use of benzodiazepines in a stent.

- Neither Punegova, Kim, nor Soykan teaching using Bz-423 in drug eluting stent media in an amount effective to inhibit restenosis. Beyond this, Applicant submits that neither Punegova nor Kim teach or suggest the feature of claim 1 that the drug-eluting stent media is coated on a vascular stem.

To respond: Kim and Ramdas obviate the compound recited in instant claim 1. Soykan teaches a description a "delivery device" includes the carrier (e.g., stent), cells that produce one or more therapeutic agents, and optional containment vehicles, as well as other optional therapeutic materials (col. 11, lines 3+). Current office action relies upon Ramdas that teaches benzodiazepine compounds as inhibitors of the Src protein tyrosine kinase. The benzodiazepine

compounds were found to have IC_{50} of 73μM and Levitzki that teaches that Protein tyrosine kinases (PTKs) play a key role in normal cell and tissue development. Enhanced PTK activity is intimately correlated with proliferative diseases, such as restenosis (abstract).

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nabila G. Ebrahim whose telephone number is 571-272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nabila G Ebrahim/
Examiner, Art Unit 1618

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618